

**Remarks**

Claims 2, 4, 16, 18, 21, 22 and 40 are currently under examination. Claim 21 is canceled herein. Claim 22 and 40 are amended herein. Support for these amendments can be found in claims 21, 22 and 40 as filed. No new matter is believed to be added by these amendments. Pursuant to the following remarks, Applicants respectfully request allowance of the claims to issue.

Supplemental IDS

A supplemental IDS is being submitted concurrently that sets forth the prosecution history of related foreign applications issued in Australia and Europe as Australian Patent No. 781134 and European Patent No. 1179061, respectively.

Rejection Under 35 U.S.C. § 103(a)

Applicants appreciate the opportunity to discuss the application telephonically with Examiners Burkhardt and Woitach on May 5, 2008. During this telephone conference, the rejection under 35 U.S.C. § 103(a) was discussed. The following remarks more specifically address this rejection.

The Office Action states that claims 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Li et al. (US Patent No. 6,638,502) in view of Restifo et al. for reasons of record and additional reasons set forth in the Office Action dated February 8, 2008. Claim 21 is canceled herein. Claim 40 is amended herein to specify that the signal sequences is an adenoviral E19 signal sequence.

On page 4 of the Office Action, the Examiner has responded to Applicants' arguments by stating that Applicants present no reasoning or evidence, other than that the E19 ss was used by Restifo et al. to express only small peptides, as to why expression of a heterologous polypeptide using the E19 signal sequence would be unexpected. Further stated in the Office Action is that a review of signal sequences (Martoglio et al., 1998) teaches the conserved characteristics of signal sequences (and the machinery that recognizes them) across eukaryotic cells. According to the Office Action, Martoglio et al. teach that: "Different signal sequences guide their passenger

proteins through apparent common pathways and can be interchanged between different proteins or even between proteins of different organisms.” The Office Action goes on to state that the prior art clearly indicates that the E19ss is functional to direct the secretion of heterologous proteins/peptides. Thus, according to the Office Action, given the teachings of the prior art, one of skill in the art could predictably use this signal sequence to direct secretion of antiangiogenic proteins from an adenoviral vector in a eukaryotic cell. Furthermore, the Office Action asserts that the totality of the prior art teaches that antiangiogenic proteins can be expressed using signal sequences other than those “naturally associated” with the antiangiogenic protein.

Applicants reiterate that Restifo et al. discloses only the expression of small peptides with the E19 signal sequence. Furthermore, other than naturally directing the expression of a 19 kD protein, the Examiner has provided no evidence that the E19 signal sequence can be utilized to efficiently express any heterologous protein, much less an antiangiogenic protein that is expressed at sufficiently increased levels to effect systemic treatment of tumors. The Examiner has also taken the position that signal sequences are interchangeable and that the functional expression of an antiangiogenic protein can be achieved with an E19 signal sequence.

Applicants respectfully disagree and point out that Martoglio et al. states that “[s]ignal sequences can differ in the efficiency by which they mediate targeting and membrane insertion.” (page 412, first full paragraph). Martoglio et al. further states that “[i]t is not yet clear how the efficiency of signal sequence function in targeting and membrane insertion is regulated. Signal sequences can have reduced affinities for targeting factors (e.g. SRP) or components at the translocation site (e.g. Sec16 complex or the translocation-associated membrane protein). Therefore, it is clear that not all signal sequences have the same efficiency or similar mechanisms of regulation. In fact, there are numerous instances where substitution of one signal sequence with another signal sequence results in reduced secretion of a heterologous protein. For example, Rowland et al. (“The effect of signal sequences on the efficiency of secretion of a heterologous phosphotriesterase by *Streptomyces lividans*” *Appl. Microbiol. Biotechnol.* 38: 94-100 (1998)) describe the secretion by *Streptomyces lividans* of a heterologous phosphotriesterase containing the native *Flavobacterium* species signal sequence. The *Flavobacterium* species signal sequence resulted in approximately a third of the total activity of the recombinant *S. lividans* culture remained cell-associated, suggesting inefficiency in the secretion process (see

page 94, second column third full paragraph). Upon replacing the *Flavobacterium* species signal sequence with a native *S. lividans* signal sequence, the strain produced more parathion hydrolase on a milligram protein per liter basis and secreted a larger proportion of its parathion hydrolase into the extracellular broth than did the strain with the native *Flavobacterium* signal sequence (see page 98, second column, second full paragraph). Therefore, it is clear that although the *Flavobacterium* species signal sequence effects secretion, it was not as efficient as a *S. lividans* signal sequence, thus showing that the signal sequences are not interchangeable.

In another example, Bird et al. ("The Functional Efficiency of a Mammalian Signal Peptide is Directly Related to its Hydrophobicity" *Journal of Biol. Chem.* 25: 8420-8425 (1990)) shows that the signal sequence of *S. cerevisiae* vacuolar protein carboxypeptidase Y (CPY) does not function in mammalian cells unless a glycine residue in the h region is replaced with a leucine (see abstract). Therefore, it is clear that one cannot utilize this signal sequence in mammalian cells without modification. Thus, simply substituting one signal sequence with another signal sequence does not always result in functional secretion.

In a further example, Belin et al. ("A two-step recognition of signal sequences determines the translocation efficiency of proteins" *The EMBO Journal* 15: 468-478 (1996)) describes the replacement of the complete N-terminal region of mPAI-2 by the equivalent region of ovalbumin, and determination of the efficiency of translocation of this chimeric protein (OVA-PAI2). Although mPAI-2 and ovalbumin are both members of the SERPIN family, replacement of the mPAI-2 signal sequence with the ovalbumin signal sequence resulted in low translocation efficiency (see page 475, second column first full paragraph). Therefore, contrary to the Examiner's assertion, one of skill in the art cannot simply assume that signal sequences can be replaced without deleterious consequences. Thus, one of skill in the art could not have predicted that replacing the signal sequence of Li et al. with the E19 signal sequence disclosed in Restifo et al. would result in sufficient expression of an antiangiogenic protein to effect systemic treatment of tumors.

Furthermore, Applicants remind the Examiner that the teachings of Li et al. are directed to local delivery (intratumoral) and the teachings of Restifo et al. are directed to small peptides fused to a signal sequence, for example, E19/P1A, that act as immunogens to elicit a T cell

response. These activated T cells were reactive against a tumor peptide and caused tumor cell lysis. Thus, it is the activated T cell that causes tumor cell lysis and not the E19/P1A fusion protein. One of skill in the art would readily recognize that the fusion proteins of Restifo et al. have no other activity than to act as immunogens and would not be considered antiangiogenic proteins. Therefore, there was no reasonable expectation that that a nucleic acid encoding the antiangiogenic protein of Li et al. operatively linked to the adenovirus signal sequence of Restifo et al. would have the properties of the claimed compositions, i.e. 1) the ability to increase circulating levels of an antiangiogenic protein; and 2) the ability to treat tumors via systemic delivery.

According to the Examiner, the new limitation in claim 40 that systemic delivery of the claimed compound results in increased levels of the antiangiogenic protein and inhibition of tumor growth is an intended use limitation. Further stated by the Examiner is that since the structure taught by the prior art could be used for the intended use of systemic delivery, it is considered that the prior art structure meets the claim limitations. Furthermore, according to the Examiner the prior art (Griscelli et al., 1998) indicates that delivering antiangiogenic proteins using adenoviral vectors results in the limitations set forth by the intended use phrase.

Applicants reiterate that even if one of skill in the art were motivated to combine Restifo et al., with Li et al., and they were not, there would be no expectation of success that delivering a viral vector comprising a nucleic acid encoding an antiangiogenic protein, for example, endostatin, linked to an adenovirus E19 signal sequence would result in sufficient expression of the antiangiogenic protein to achieve tumor growth inhibition via systemic administration. Nothing in the prior art would lead one of skill in the art to believe that this specific signal sequence would achieve these results. Nothing in Restifo et al. or Li et al., alone or in combination, suggest arriving at a composition that reduces tumor growth by targeting endothelial cells systemically. Therefore, Applicants maintain that one of skill in the art would not have been motivated to arrive at the claimed structure. Applicants respectfully point out that Griscelli et al. does not disclose a nucleic acid encoding an antiangiogenic protein operatively linked to the adenovirus E19 signal sequence. Therefore, Griscelli et al. does not have the structure of the claimed compositions. Furthermore, although the Examiner believes that signal sequences are readily interchangeable, for the reasons stated above, one of skill in the art could

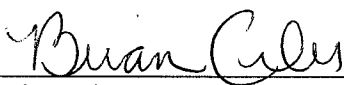
not predict that replacing the signal sequence utilized by Griscelli et al. with an E19 signal sequence would result in systemic treatment of tumors.

Therefore, for the reasons set forth above, Applicants believe that claims 2, 4, 16, 18, 21, 22 and 40 are unobvious over Li et al. in view of Restifo et al. Thus, Applicants respectfully request withdrawal of this rejection.


Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment submitted via EFS Web in the amount of \$1,050.00, representing the fee for a large entity under 37 C.F.R. § 1.17(a)(3), and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

  
P. Brian Giles, Ph.D.  
Registration No. 57,896

BALLARD SPAHR ANDREWS & INGERSOLL, LLP  
Customer Number 36339  
(678) 420-9300  
(678) 420-9301 (fax)

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